21. A medicinal product for the treatment and prevention of AIDS containing the cyclosporin according to claim 17.

REMARKS

In the Examiner's Office Action in date of October 10, 2002, the drawings are objected to under 37 CFR 1.84(h) (5) because "*figures 1 to 3 show modified forms of construction in the same view*".

This rejection is respectfully traversed.

Figure 1, as indicated at page 7 line 1 of the description, represents the general chemical formula of the novel cyclosporin claimed in the present specification.

Figure 2 represents a NMR H1 spectrum registered between 10 and 0 ppm of a cyclosporin according to the invention, wherein the residue in position 4 is an N-acylated aminoacid.

Figure 3 represents an enlargement of the above spectrum in the domain of 8.75 to 6.75 ppm.

Thus, the figures do not show modified forms of construction in the same view and it is respectfully requested that the Examiner's objection in this regard be withdrawn.

The Examiner indicates that the applicant's submission of IDS is incomplete since it contains no legible copies of each US and foreign patent and each publication or that portion which caused it to be listed as cited in the list of the submitted IDS.

This objection is respectfully traversed.

Applicant fails to understand the Examiner's objection, since the IDS submitted on March 29, 2001 indeed lists the prior art referred to by the Applicant as well as that cited

in the search report prepared by the European Patent Office and provides a copy of all references cited therein.

Applicant respectfully requests the Examiner to reconsider this objection. Examiner apparently refers to an earlier IDS filed June 9, 2000, not to the one submitted on March 29, 2001.

The Examiner is respectfully requested to consult the records and, of course, if any error was made by the Applicant in submitting the IDS of March 29, 2001 then those errors will be promptly corrected.

Furthermore, Applicant provides herewith a legible copy of the article "The Chemistry of Cyclosporine" (Wenger, in Peptides (1996) p. 173-178). This article is cited at p. 8, l. 12 and l. 19 of the specification.

The Examiner has objected to the disclosure because of a certain number of informalities. Applicant hereby submits corrected pages No. 1, 3, 5, 6, 17.

In particular, at page 1, line 6, the term "Cs" has been changed to "cyclosporins".

It is respectfully submitted that the mention of "Gag" at page 3 line 25 is perfectly comprehensible to all persons skilled in the art and does not require any further explanation. In this respect, please see pages 598-599 of the general text book "Genes" by Benjamin Lewin which refers to the gag-pol-env genes of retrovirus.

As far as page 4 line 7, the expression "HIV-1" is concerned, please see page 3, line 19 where this expression is set out in full.

As far as page 6 lines 2, 3 and 4 are concerned, please see page 1 line 25 to page 2 line 7 where the abbreviations for MeBmt, Abu, Nva, Sar are given in full.

It is respectfully submitted that as far as the other expressions such as MeSer, Me-Ala, OAcyl, etc are concerned, these are normally used expressions by the person skilled in the art in terms of aminoacid chemistry and do not need to be explicited further.

The expression at page 7 line 6 CaN refers to calcineurin which is indicated at page 3 line 14.

aa^4 has been explained at p. 6, l. 11-13. OtBu refers to a tertio-butyl ether.

CEM-SS is a well-known cell line used for testing anti-HIV products. As evidence of this, please see the abstract attached herewith (Cell Mol. Biol.) as well as an article found by the Applicant's Patent Attorney on the web simply by entering "CEM-SS" as a query in the Alta-Vista search site.

Appropriate correction has been made at page 3 lines 12 to 13, but not as suggested by the Examiner, and at page 17 line 19, as suggested by the Examiner.

The Applicant has made a good faith attempt to rectify all informalities, even those not mentioned by the Examiner, in the specification, and hopes that the specification as now amended will fully comply with the Examiner's requirements.

Claims 8 to 14 are rejected under 35 USC 112 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the subject-matter which Applicant regards as the invention.

This rejection is respectfully traversed.

New claims 15 to 21 have been amended so as to overcome the Examiner's objections.

Thus new claim 15 corresponding to previous claim 8 has been amended in so far as the word "or" has been inserted each time there is a choice in the type of residues. Furthermore, it is respectfully submitted that claim 1 is not unclear with

respect to the expression (N-R)aa which in fact refers to N-alkylation at the position 4 aminoacid since it is perfectly clear from the description, as well as from Figure 1, that this is what is meant.

The same explanation is provided for previous claims 9 and 10.

In previous claim 12 (new claim 19), the expression "wherein it is" has been eliminated.

In previous claims 13 and 14 (new claims 20 and 21), the recitation "intended" is eliminated and the comma in previous claim 13 has been deleted as suggested by the Examiner.

Claims 8 to 14 are rejected under 35 USC 102(e) as being anticipated by Steiner J.P. et al. (US patent No. 6,444,643).

This rejection is respectfully traversed.

The cyclosporins of the present invention differ from those described in the Steiner patent precisely with respect to the fact that the residue in the number 4 position (referred to as the Z residue in the present patent application and as R_4 in column 10 of the Steiner patent) is not simply a methylated aminoacid but rather an amino acid having an N-alkyl group greater than methyl. R_4 in column 10 line 13 and also line 54 of the Steiner patent is in fact a methylated aminoacid as is clear from the expression at column 10 line 13, "*R_4 is an N-methylated aminoacid residue…*" and the expression at column 10 line 54 where it is indicated that "*R_4 is methyl leucin, methyl Valine, methyl homo-Alinine or methyl(a-methylthreonine)*".

Furthermore, it is very clearly indicated at page 6, line 11 and following of the present specification that by replacing the natural methyl leucin group in position 4 of cyclosporin by an N-alkyl aminoacid group where alkyl is

greater than methyl, the anti-HIV 1 activity of these derivatives is improved.

The cyclosporins of the present invention, as further indicated at page 3, line 17 of the present application, provide considerable HIV 1 inhibitory activity without the undesirable immunosuppressive activity of cyclosporin A. The Examiner's reference to the passage at column 11 line 18 of Steiner does not disclose the compositions of the present application since it again refers to a methylated position 4 residue.

Furthermore the article by Papageorgiou, cited in the Steiner reference at column 11 line 22, is in fact already mentioned in the present specification at page 5 line 8, where it is and it is indicated that this substance has a reduced anti-HIV activity.

In view of the above, it is respectfully submitted that the Steiner patent in fact does not anticipate the subject-matter of claims 15 to 21 of the present application.

Claims 8 to 14 are rejected under 35 USC 103(a) as being obvious over Ko et al. (US patent No. 5,767,069) taken with Steiner et al.

This rejection is respectfully traversed.

Ko et al. teaches a cyclosporin having a methylated aminoacid in position 4. As already indicated above, there is absolutely no teaching in Steiner to change the methylation into a longer alkyl group.

Applicant can find no basis in the Steiner application for the Examiner's assertion at pages 8-12 of the pending Office Action that Steiner teaches that position 4 is N-ethyl Valine.

In fact, it is clear from the specification of the present patent application that precisely the increase in the number of the alkyl group leads to a new cyclosporin which has

greater anti-HIV activity, at the same time having lower immunosuppressive activity of cyclosporin A. Knowing that HIV is an immunosuppressive disease, it is extremely important to lower the immunosuppressive activity of any drug that is given as a treatment for HIV. The Applicant has the merit of having designed a new cyclosporin which has increased anti-HIV activity simultaneously with decreased immunosuppressive activity. This is clearly novel and unobvious over the cited prior art.

In view of the foregoing it is respectfully submitted that the application is now in proper form for allowance.

Respectfully submitted.

Roland M. WENGER et al

Jan. 31, 2003
Date

By: Michael O. Sturm
Michael O. Sturm
Reg. No. 26,078

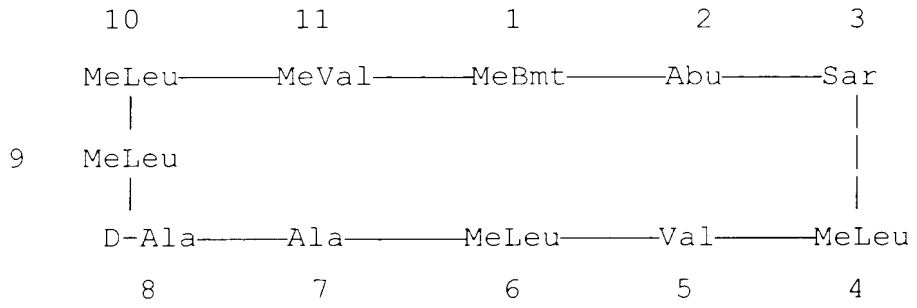
STURM & FIX LLP
206 Sixth Avenue, Suite 1213
Des Moines, Iowa 50309-4076
Telephone: (515) 288-9589
Telefax: (515) 288-5311

Novel cyclosporin having an improved activity profile

The present invention relates to a novel cyclosporin (Cs), the pharmaceutical use thereof and to a pharmaceutical composition containing it.

Cyclosporins are a class of cyclic poly-N-methylated undecapeptides having several pharmacological activities; in particular, they are immunosuppressants, anti-inflammatories, anti-parasitic agents, drug resistance suppressors (anti-MDR) and anti-viral agents. The first cyclosporin isolated from a fungal culture is cyclosporin A which is found in the natural state and which is represented by the following formula:

Structure of cyclosporin A



Abu = L-α-aminobutyric acid

Ala = L-alanine

MeBmt = N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine

Cyclosporin A (CsA) isolated 20 years ago from Tolypocladium inflatum has considerable immunosuppressive activity. It has revolutionised organ transplantation and is commonly used in the treatment of autoimmune diseases. For a recent review of the use of CsA and its mechanisms of action, see Wenger et al: Cyclosporine Chemistry, Structure-activity relationships and Mode of Action, Progress in Clinical Biochemistry and Medicine, Vol. 2, 176 (1986).

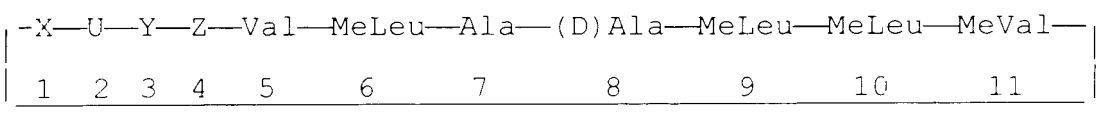
The therapeutic effect of CsA results mainly in the selective suppression of the activation of T lymphocytes. This immunosuppressive activity is explained by the fact that CsA binds to an intracellular proteic receptor cyclophilin A (CyP), forming a CyP-CsA complex which interacts with calcineurin (CaN) and thus inhibits its phosphatase activity. Thus, the transcription of families of genes exhibiting precocious activation will be blocked (cf. O'Keefe, S.J; Tamura, J; *Nature* 1992, 357, 692-694).

The present invention provides the production of a novel cyclosporin with considerable HIV-1 (human immunodeficiency virus) inhibitory activity and not having the immunosuppressive activity of CsA.

The mode of infection of HIV type 1 is unique amongst the retroviruses because it requires the specific incorporation into its virion of the cellular protein CyP which interacts with the polyprotein Gag (cf. Eltaly Kara Franke, Bi-Xing Chem. Journal of Virology, Sept. 1995, vol. 69 no. 9). It is well known that CyP binds to CsA and CaN in

derivatives in position 3 such as, for example, (D)-MeSer^3-(4-OH)MeLeu^4 cyclosporin. This substance has a better affinity for CyP but only has limited anti-HIV activity compared with the reference derivative MeIle^4-Cs(NIM 811). The more hydrophilic nature of this substance prevents it penetrating the cells and the organism. This is reflected directly in the reduced anti-HIV activity of this substance (cf. Christos Papageorgiou, J.J. Sanglier and René Traber - *Bioorganic & Medicinal Chemistry Letters*, Vol, 6, No. 1, pp. 23-26, 1996).

The substances described in this invention have the dual advantage of retaining the same affinity for CyP as that observed with [(4-OH)MeLeu^4]-Cs or cyclosporin A whilst having anti-HIV activity which is identical to or greater than that of the reference derivatives (MeVal^4-Cs or MeIle^4-Cs) and appreciably greater than the anti-HIV activity of cyclosporin A or of (4-OH)MeLeu^4-Cs. The object of the invention is to provide a novel cyclosporin which does not have the immunosuppressive activity of CsA and has an improved profile of activity. This new family of Cs is characterised by the formula (I):



(I)

wherein:

X is -MetBmt or 6,7-dihydro-MeBmt-

U is -Abu, Nva, Val or Thr

Y is Sar or (D)-MeSer or (D)-MeAla or (D)-MeSer (OAcyl)

Z is (N-R)aa where aa = {Val, Ile, Thr, Phe, Tyr, Thr (OAc), Thr (OG_1), Phe (G_2), PheCH_2(G_3) or Tyr (OG_3)} with

R = {alkyl > CH_3};

G_1 = {phenyl-COOH, phenyl-COOMe or phenyl-COOEt};

G_2 = {CH_2COOH, $CH_2COOMe(Et)_4$, $CH_2PO(OMe)_2$ or $CH_2PO(OH)_2$};

G_3 = {$PO(OH)_2$, $PO-OCH_2CH=CH_2$), CH_2COOH or $CH_2COOMe(Et)$}

Thus, by replacing the natural MeLeu group in position 4 by an N-(alkyl)aa group (where alkyl > CH_3), the anti-HIV 1 activity of this derivative is improved.

The new cyclosporin molecule thus obtained offers the unexpected and surprising advantage of having much better stability towards metabolisation than all the other cyclosporins known hitherto.

This new molecule is much more resistant to the phenomena of oxidation and degradation which take place in the cell. Consequently, the "in vivo" life of this new N-alkyl aa Cs is particularly prolonged.

Moreover, this new N-alkyl aa^4 cyclosporin has high affinity for CyP and has anti-HIV activity which is equal to or greater than the best existing cyclosporins.

response but retain their antigenicity. The IC_{50} calculated in the MLR test is compared with the IC_{50} corresponding to CsA in a parallel experiment. The IR index is thus found, this being the ratio of the IC_{50} of the MLR test of the derivatives over the IC_{50} of cyclosporin A.

As with the binding index (BI) above, a value of 1.0 for the IR means an activity similar to CsA. Similarly, a lower value means better activity and a value greater than 1.0 shows that the activity of the compound is lower than that of CsA.

An IR value of > 20 shows that the substance is not immunosuppressive. The immunosuppression values of the derivatives are given in Table I.

Table II describes the percentage protection during infection with HIV of a CEM-SS cell line. The protection of this line in the presence of a Cs derivative is compared with the infection of a line cultivated in the absence of Cs (reference control). A mean value is established at a concentration of the derivative of $2x10^{-6}$ molar. This anti-HIV activity was measured by the NCI (National Cancer Institute) in Washington in the USA.